ALCOHOL-INDUCED HYPERTENSION: MECHANISMS, COMPLICATIONS, AND CLINICAL IMPLICATIONS

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Alcohol abuse is a frequent contributor to elevated blood pressure and may be the most common cause of secondary hypertension. The mechanism of this association is unknown. In most cases, the blood pressure elevations are reversible and return to normal upon discontinuation of alcohol use. Even though transitory, such hypertension cannot be considered benign, or inconsequential, since it may be contributory to the increased prevalence of cardiovascular disease observed in problem drinkers.

Excessive alcohol intake is a more frequent contributor to elevated blood pressure than is generally appreciated, and may be the most common cause of secondary hypertension. The association between alcohol consumption and hypertension was first reported in 1915 by Lian[1] who, after studying a group of French servicemen, found the frequency of hypertension (≥ 150/100 mmHg) to be about three times higher in heavy drinkers than in moderate drinkers. Since then, epidemiologic studies[2-5] have confirmed this association.

In studies in which mean blood pressure levels were reported according to alcohol-use categories, blood pressure elevations were 1.6 to 10.9 mmHg higher in the higher alcohol-use groups than in the low- or no-use groups. When dose-response relationship was evaluated, the subjects with the highest alcohol intake had the highest blood pressures. The magnitude of the increase in blood pressure in heavy drinkers averages about 5 to 10 mmHg, with systolic increases nearly always greater than diastolic increases. In the Framingham cohort,[2,6] there was an increase of 7 mmHg in mean arterial pressure when heavy alcohol users were compared with all others, but no dose-response relationship was found.

When the association between alcohol con-

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sumption and blood pressure is expressed in terms of prevalence of defined high blood pressure, hypertension (BP ≥ 160/95 mmHg) is 1.6 to 2.4 times more prevalent in "heavy" or "problem" drinkers than in various control groups reporting less or no alcohol use.[4-6] A "heavy" or "problem" drinker is usually defined as a person who consumes more than five drinks each day, one drink being 1.25 oz of whiskey (40 percent alcohol, or 80 proof), 12 oz of beer, 5 oz of table wine, or an average-sized cocktail, all of which contain about 13 gm of alcohol.[7] A "moderate" drinker is usually defined as one who consumes an average of one to two drinks daily.

In men, the relationship between alcohol consumption and average systemic blood pressure is linear over the range of moderate to heavy use. In women, however, the relationship is U-shaped.[4,6,8] Women who consume moderate amounts of alcohol have lower mean blood pressures than women who are teetotalers. Average systemic blood pressure in women correlates inversely with alcohol consumption of up to 20 mg/day. However, average systolic blood pressure is higher in women who consume more than 30 gm/day than in women who consume less.

Studies of alcoholics during detoxification also support this association with findings of blood pressures of 140/90 mmHg or higher in more than 50 percent of alcoholics admitted for detoxification,[9] and blood pressures of 160/95 mmHg or higher in one-third of alcoholics admitted for detoxification without delirium tremens.[10] Blood pressure returns to normal in approximately 70 percent of alcoholics after detoxification and remains normal, if patients remain abstinent. Upon reintroduction of alcohol use, blood pressures again become elevated.[11] About 10 percent of alcohol abusers have persistent hypertension even during sustained abstinence, which may be a reflection of the coincidental occurrence of essential hypertension.

MECHANISM

The mechanism of the association between alcohol and hypertension is unknown. Even though alcohol users tend to differ from nonusers in terms of age, sex, cigarette smoking, and obesity, the association of alcohol and hypertension is not dependent on these confounding variables. This relationship is also independent of race, serum cholesterol value, educational achievement, social class, and coffee consumption.[9,12,13]

Some investigators[6] have suggested that the association between alcohol and hypertension is related to the temporal sequence of alcohol use and blood pressure measurement. Since many community programs require an overnight or twelve-hour fasting period, alcohol withdrawal, albeit subclinical, may be occurring. Similarly, patients may abstain or diminish alcohol intake before visiting a clinic or physician. Thus, the observed elevations in blood pressure could be due to excessive central-nervous-system excitability and adrenergic discharge associated with the withdrawal period. Catecholamine excretion has been found to be elevated during acute and chronic alcohol administration.[14] These patients show still further increases, especially in urinary epinephrine, with abrupt withdrawal. Plasma norepinephrine levels are highest 13-24 hours after alcohol cessation. These observations suggest stimulation of adrenal medullary secretion, as well as changes in sympathetic nervous system activity.

In contrast to the above reports, two recent studies reported normal plasma catecholamines. Arkwright, et al[15] measured basal and stimulated plasma norepinephrine and epinephrine in 30 moderate drinkers and 30 age-matched nondrinkers. Despite finding a significantly higher blood pressure in drinkers (9-7 mmHg), there were no differences found in plasma catecholamines. Ibsen, et al[16] compared plasma norepinephrine values in heavy and low-moderate chronic alcohol users. These investigators found no statistically significant differences. No comparison to normal values was made. Both blood pressures and pulse rates were higher in the higher intake group. These studies indicate that elevated blood pressures in chronic alcoholics can be maintained by mechanisms other than elevated plasma catecholamines.

Ethanol and its metabolites act initially as vasodilators, although vasoconstriction has been observed in some regional circulations following the feeding of ethanol to rats for two to six weeks. Altura[17] observed that these animals developed in-

creased tolerance to the vasodilating actions of ethanol. Moreover, such rats would demonstrate an exaggerated sensitivity to the vasoconstrictive effects of epinephrine.

Clark, et al[10] found that a cold pressor test performed on alcoholics with transitory hypertension (at a time when their blood pressures and catecholamine levels were normal) produced an exaggerated response in blood pressure, heart rate, and catecholamine levels. An atypical adrenomedullary response, with elevated levels of epinephrine and norepinephrine, was also observed. However, the augmented catecholamine response per se did not explain the increase in blood pressure. Ordinarily, it appears that compensatory autonomic reflexes may preserve blood pressure following acute alcohol intake without significant changes in hemodynamics. With long-term alcohol use, however, an abnormality in vascular responsiveness with vascular hyperactivity may occur, and could be responsible for the observed hypertension. Similarly, other vasoactive substances (eg, prostaglandins, angiotensin II, histamine, intestinal and opioid peptides), a neuro or neurohumoral mechanism could be responsible.

Another possible mechanism is that the blood pressure elevation observed during detoxification represents a rebound phenomenon, as has been observed in man with the abrupt cessation of vasodilator therapy.[18] Since even the heaviest abusers of alcohol have frequent periods of abstinence, though perhaps brief, these patients may be in a state of chronic withdrawal. The chronic abuser may be in a perpetual state of alternating between acute intoxication and withdrawal. Therefore, blood pressures observed during the withdrawal period may correlate with chronic blood pressures.

An effect on the renin-angiotensin-aldosterone system has also been postulated. Beevers, et al[19] reported elevated plasma renin activity in 28 of 48 chronic alcoholics and raised plasma aldosterone in eight. All values returned to normal in seven days following the cessation of drinking. These investigators attributed the elevated plasma-renin activity to low sodium intake, although they also noted an increased sympathetic nervous system activity (high dopamine beta-hydroxylase values), suggesting an adrenergic mechanism. Actual hormone levels, normal values, and statistical analyses were not performed.

Linkola and co-workers[20] compared plasma-renin activity, plasma-aldosterone, and plasma-cortisol in a control group. After ethanol loading, seven young healthy supine men were put on a constant sodium and potassium diet. Plasma aldosterone levels declined during the initial three hours of ethanol loading in six of the seven subjects, but rose approximately twofold over control levels during the subsequent three hours as ethanol levels were declining. No changes were observed in plasma-renin activity or plasma-cortisol levels during the first three hours, but plasma cortisol was noted to rise at the same time as plasma aldosterone. The correlation of plasma aldosterone and plasma cortisol rises suggests stimulation by adrenocorticotropic hormone. Plasma-renin activity did not become elevated until 14-16 hours later, during the hangover phase, at a time when plasma aldosterone was unchanged. Thus, it appears that under some circumstances, the renin-angiotensin system may be activated during the chronic and withdrawal phases of alcoholism.

The mechanisms of the observed changes in the renin-angiotensin-aldosterone system are uncertain. A role for adrenal corticotropic hormone is suggested by the data of Linkola, et al. Sympathetic nervous system activation may stimulate renin release, but the data are inconclusive. Cortisol may be in part responsible, since plasma-cortisol levels increase following acute alcohol ingestion, and a Cushing's-like syndrome (including hypertension) has been described in chronic alcoholics. Aldosterone secretion does not appear to be significantly affected by alcohol.

CLINICAL IMPLICATIONS

According to estimates, about two-thirds of adults in affluent countries use alcohol to some extent and approximately 10 million Americans (7 percent of the adult population) can be classified as heavy users.[21-22] These calculations have led several investigators to estimate that excessive alcohol consumption may be a significant contributor to elevated blood pressure in 10 to 30 percent of patients with essential hypertension.[13] If

these estimates are true, alcohol abuse could be, by far, the most common cause of secondary hypertension. Furthermore, the only treatment required in most instances would be abstinence. Hypertension due to alcohol abuse appears to be reversible, at least temporarily. Such hypertension cannot be considered benign, however, since it may contribute to the increased risk of cardiovascular complications observed in problem drinkers.

Stroke

The incidence of cerebrovascular accidents is higher in alcoholics than in nondrinkers. The Yugoslavian Cardiovascular Disease Study showed a threefold increase in stroke mortality in heavy drinkers compared with infrequent drinkers.[23] Alcohol abuse appears to be especially prevalent in stroke patients less than 50 years of age.[24] In the Kaiser-Permanente study, Klatsky found a correlation between hypertension and stroke with increasing alcohol usage.[4,9] In the Framingham study, alcohol consumption did not correlate with the incidence of stroke, but there was a trend in that direction when alcohol intake exceeded fourteen ounces per month.[25] In rural Japanese communities, Rubin[25] found that the risk of stroke was higher in those who consumed alcohol daily than in occasional consumers or nondrinkers. Data from the Honolulu Heart Program showed that the risk of stroke correlated with increasing amounts of alcohol consumption.[26] In the Honolulu Heart Program data, the positive association was true for intracranial hemorrhage, but not for cerebral infarction which could not be explained by the relationship of alcohol and hypertension. The authors hypothesized that this may reflect an alcohol-associated thrombocytopenia and/or impaired platelet function which would enhance bleeding in cerebrovascular lesions, leading to an increased incidence of hemorrhagic stroke. Thus, although stroke is more common in alcoholics, and in some studies the incidence of stroke correlates with the presence of hypertension, a cause-and-effect relationship has not been demonstrated.

Coronary Artery Disease

The relationship between alcohol consumption and coronary artery disease has received considerable attention. Much of this is due to the possibility that moderate intake may decrease the risk of myocardial infarction and death from coronary heart disease. Several epidemiologic studies have shown a favorable influence of moderate alcohol consumption on coronary heart disease. Excessive consumption, on the other hand, appears to increase the risk of this disease.

Klatsky and colleagues,[4] on reviewing the Kaiser-Permanente epidemiologic study of myocardial infarction, found that teetotalers were at greater risk than moderate drinkers. Yano and co-workers[27] reported similar findings in Japanese men living in Hawaii. They found a negative association between moderate alcohol consumption (up to 60 mL[2 oz]/day) and the risk of nonfatal myocardial infarction and death from coronary artery disease. They attributed this finding to elevated serum levels of high-density lipoprotein cholesterol associated with alcohol consumption. This apparent protective effect was related to the amount of alcohol consumed ($\leq$ 2 oz/day), not to the type of beverage ingested.

In contrast, alcoholics have been found to be at increased risk of coronary heart disease. D'Alonzo and Pell[5] found that problem drinkers were at high risk for coronary heart disease; however, confounding variables were not controlled in their study. Wilhelmsen[28] and Dyer,[3] et al used multivariate analyses that took into account a history of smoking and the presence of hypertension. Results showed that problem drinkers had a higher mortality rate and risk of myocardial infarction than moderate drinkers.

Thus, alcohol appears to affect cardiovascular mortality in a bimodal fashion, with nondrinkers and abusers at higher risk of coronary heart disease than moderate drinkers. Since hypertension is known to be a major risk factor for coronary heart disease, a contributory role of alcohol in some patients can be postulated.

Cardiomyopathy

Electrocardiographic signs of left ventricular hypertrophy and left atrial enlargement are more commonly found in alcoholics with transitory hy-

pertension than in those without hypertension. These changes could be early precursors of alcoholic cardiomyopathy. The impact of hypertension on heart muscle may be particularly detrimental in the setting of chronically elevated plasma catecholamine levels, alcohol-induced myocardial depression, and acetaldehyde-associated interference in cardiac protein synthesis.[4] Alcoholic cardiomyopathy may, therefore, be a consequence of hypertension occurring in the presence of metabolic abnormalities in alcoholics.

CONCLUSIONS

Alcohol usage is a more frequent contributor to hypertension than is generally appreciated. It appears to be transitory in most patients, but is not benign. Hypertension might result in target-organ injury and could be the causal link to the increased incidence of stroke and coronary events observed in problem drinkers, as well as a contributor to the pathogenesis of alcoholic cardiomyopathy. Because of its transitory nature, alcohol-associated hypertension may go unrecognized, or may be dismissed as inconsequential. Thus, regrettably, a major potential cause of cardiovascular morbidity may go untreated.

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